REMARKS

Replacement of Drawings

Applicants include herewith a set of new drawing for review by Examiner Grun. The drawings meet all the requirements of 37 CFR §1.84.

Rejection of Claims and Traversal Thereof

In the June 20, 2005 Office Action,

claims 1-14 and 21-24 were rejected under 35 U.S.C. §112, first paragraph for numerous reasons; and

claims 1-14 and 21-24 were rejected under 35 U.S.C. §112, second paragraph.

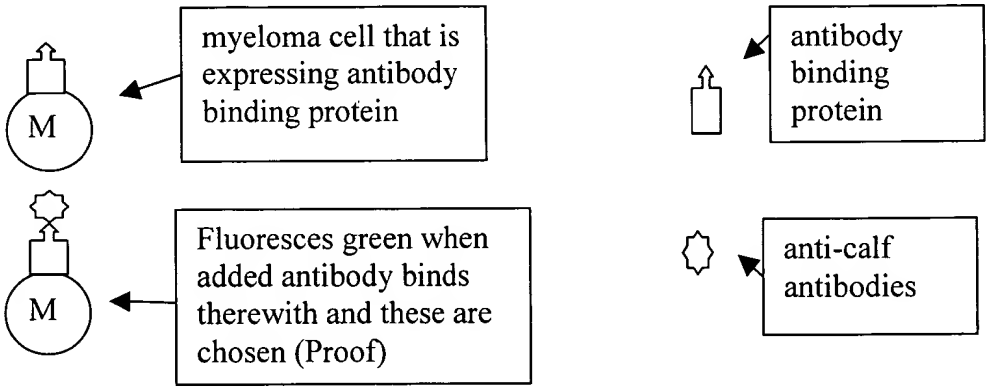
These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under 35 U.S.C. §112, first paragraph

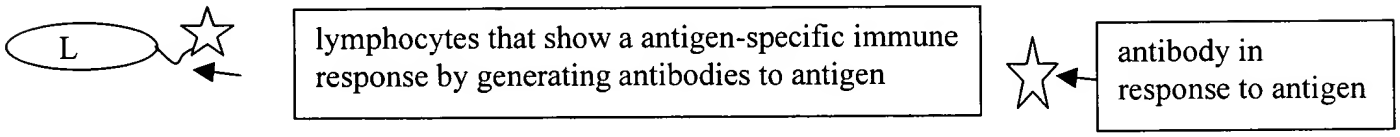
Claims 1-14 were rejected under 35 U.S.C. §112, first paragraph. According to the Office, the disclosure fails for several reasons. For completeness, applicants will address each of the Office's remarks and contentions individually. However, before the rejections are addressed, a complete understanding of applicants' invention is in order along with a visual representation.

Initially, a myeloma cell is transfected with an expression vector that includes a nucleotide sequence for an "antibody binding protein" which preferably includes a signal peptide, an antibody-binding site independent of the specificity site for an antibody and a membrane anchor. The myeloma cells express the "antibody binding protein" and the ones that

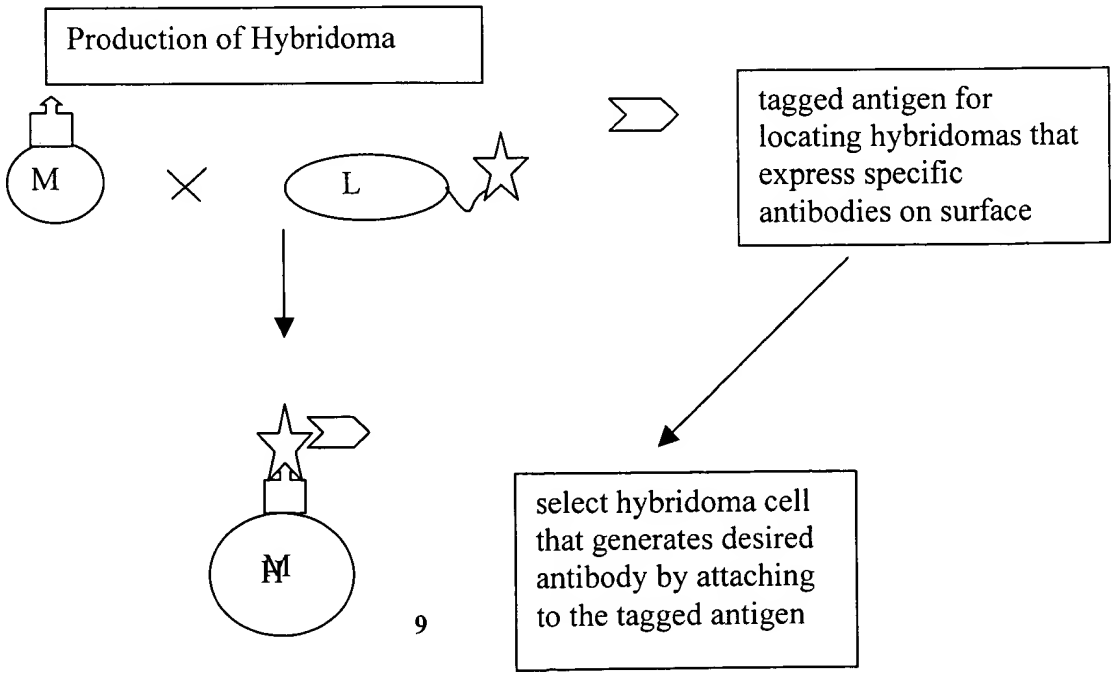
successfully express such "antibody binding protein" are determined by contacting the myeloma cells with FITC labeled antibody (tagged). This antibody will bind to the antibody-binding site, as described above. If the myeloma cell fluoresces, then the tagged antibody has bound to the antibody binding site and intuitively the antibody binding protein has been expressed on the surface. Normally myeloma cells do not express antibodies or "antibody binding proteins" so the myelomas that are fluorescing have a binding complex formed by the "antibody binding protein" and the bound antibody.



Next mice are immunized with a specific antigen and blood from the mouse is tested for the production of antibodies to the specific antigen. The spleen cells are removed from immune responsive mice and lymphocytes isolated.



The lymphocytes are fused to the myeloma cells to form a hybridoma cell.



The tagged specific antigen for locating the hybridomas that express desired antibodies is generated by constructing hexapeptides with N-terminal biotin connected to the C terminal amino acids of the protein used as the specific antigen used to immunized the mice in the previous step. This tagged specific antigen

tagged antigen for locating hybridomas that express antibodies on surface

binds with the hybridomas that express the antibody/antibody binding protein complex. These complexes will fluoresce and can easily be selected. Depending on the specificity of the antibody, the affinity for the tagged antigen will certainly be different. Affinity testing is conducted to determine the hybridomas that generate antibodies having the greatest specificity for the tagged specific antigen.

Clearly, this is a much simpler method than anything in the prior art because the need for separate wells is eliminated and the hybridomas can be cultured in one pot and selection occurs by isolating the hybridomas that fluoresce. This fluorescing is due to the fact that the antibody binding protein is securing holding the antibody on the surface and then by introducing the tagged antigen, the preferred hybridoma will be securing attached thereto. Notably, the tagged antigen can be secured to a surface and the hybridoma medium passed thereby.

According to the Office, claims 1-14 and 21-24 do not provide an adequate written description of the invention and fail to adequately teach how to make and/or use the invention. Applicants vigorously disagree. Clearly, the explanation set forth above and in the specification including the described examples provide to one skilled in the art the specifics of the method and the results.

The Office seems to be concerned that one would not be able to identify and specifically separate the secreting cells from a population of cells that are all capable of binding the secreted product. Applicants are confused by the question, and assume the Office is discussing hybridoma cells, but will attempt to show that one skilled in the art is not concerned regarding this matter because by the time the fluorescing test is completed all hybridoma cells that do not secret have not survived.

Initially, we know that the lymphocytes cells from the spleen used in the production of antibodies to a specific antigen have no mechanism to express antibody binding proteins because the cells have not been transfected with the necessary expression vector. Next, the myeloma cells do not produce antibodies so this is not an issue.

It is well known that when hybridoma cells are grown and maintained in a HAT medium, whether in separate wells with or in one big pot, they have a unique character and they will not survive unless a successful fusion of the myeloma cell and lymphocyte occurs. Clearly, B-lymphocytes will die in a few weeks in a HAT medium and mutated myeloma cells will not grow in HAT medium. However, hybridoma cells do grow on the HAT medium because the B-lymphocytes' fusion repairs the mutated myeloma and thus only cells that generate antibodies and the antibody binding protein will survive. Clearly, a viable hybridoma has to express both the antibody binding protein from the myeloma cell and the antibody from the spleen cell. As stated in the specification at page 11, the cell fusion mixture is cultured in a HAT medium and it is well known in the art that unfused myeloma cells cannot grow in HAT because they lack HGPRT and unfused normal spleen cell cannot grow for any length of time because they have a limited life span. However, successful fusion produces a hybridoma cell that is able to generate both the antibody binding protein with an antibody adhering to the antibody binding protein. If the proper fusion does not occur, then it is highly unlikely that the hybridoma cell will survive to generate either the antibody binding protein or the antibody.

It is well settled in the law that the disclosure includes not only that which is expressly set forth in words, but also that which would be understood by persons skilled in the art. As such, applicants may begin at the point where the invention begins, and describe that which is new. That which is old and well known is as if written out in the patent. Clearly, applicants should not have to explain to one skilled in the art the logistics of successful fusions to generate hybridoma cells that grow indefinitely because the spleen cell partner supplies HGPRT and the myeloma partner is immortal.

Thus, there is really no question regarding the problem proposed by the Office, that being, the ability to select the desired producer cell(s) from the population because one would be unable to identify and specifically separate the secreting cell(s) from a population of cells which are all capable of binding the secreted product.

As for the viable hybridoma cells, it should be noted that expressed antibodies and antibody binding protein expressed on the cell surface are processed in the call through the same exocytic pathway. This pathway starts in the lumen of the endoplasmatic reticulum (ER) for the antibodies to be secreted. The antibody binding proteins are anchored on the membranes of the ER pointing towards the lumen. This spatial and temporal proximity leads to expression of antibody bindings proteins on the cell surface with the prebound antibody originating from the same cell. The natural high affinity and the designed high avidity of the antibody binding proteins towards the antibody makes its dissociation in the short time period highly unlikely.

Again because of the requirement of each type of cell comprising the hybridoma cell it is highly unlikely that any cells will survive that do not express the antibody attached to the antibody binding protein. However, in the case an aberrant hybridoma cell does not produce its own secreted antibodies and expresses the antibody binding proteins on its surface in unbound form, the binding of the antibodies secreted by the other cells present in the mixture can be easily distinguished and separated from each other in the subsequent

analysis (e.g. FACS) upon binding of the labelled or immobilized antigen. Separation of such cells by FACS is clearly known by those skilled in the art.

The tagged specific antigen is then contacted with the hybridomas and the hybridomas bind to the tagged antigen by the bound antibody are selected. As stated above, these hybridomas having antibodies specific for the antigen, have different affinities and this can be easily determined by one skilled in the art. The result is----------an easily method of producing and selecting hybridomas without the enormous work of the previous methods.

Further, applicants submit that one skilled in the art after reading the specification would clearly understand that the myeloma cells are engineered in order to express a large amount of antibody binding proteins on their surface. Thereby, antibodies are trapped on the surface of their descendent hybridoma cells that now are easily sorted in FACS, obviating most of the laborious screening and subcloning needed in conventional hybridoma technology. Sorting by FAC provides for quick identification of hybridomas through different fluorescence patterns. Monoclonal antibodies, tagged with a fluorescent antigen (typically fluorescein or phycoerythrin), are bound specifically to the cells and as the individual cells pass through a laser light, the light is scattered, and the fluorescent dye becomes excited by the laser beam causing the tagged cells to emit fluorescence. Photocells then send signals to the CPU characterizing each of the cells. Cells that display the desired "photo characteristics" are collected. (Clearly, the photo characteristics of the aberrant cells discussed herein above can be distinguished at this point). The examples set forth in the specification clearly describe the present invention.

Notably, the Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992). Insofar as the written description requirement is concerned, that burden is discarded by "presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. *In re Wertheim,* 191 USPQ 90 (CCPA 1976). Further, if the specification contains a description of the claimed invention, albeit not in

ipsis verbis, then the Office, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient. Applicants assert that one of ordinary skill in the art would find that the present specification provides a clear and concise description of the present invention.

Accordingly, applicants respectfully request this rejection under 35 U.S.C. §112, first paragraph for lack of written description be withdrawn.

2. Claims 1-6 and 9-14 were rejected under 35 U.S.C. §112, first paragraph, because, according to the Office, the specification does not reasonably provide enablement for expression of cell-surface antibody binding proteins, generally other than those expressed by the particular exemplified expression vectors which function in the invention. Thus, the Office wants to limit the present invention to the three specific plasmids described in the specification.

The test for enablement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. See *United States v. Telectronics, Inc.,* 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 109 S.Ct. 1954 (1989); *In re Stephens*, 188 USPQ 659, 661 (CCPA 1976).

In making a rejection on the ground of nonenablement, the Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. See *In re Wright,* 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). The Office has not met this burden. Firstly, techniques for transfecting and expression of DNA in a cell are not considered to be unpredictable technologies. These techniques are well known and one skilled in the art can easily determine the effectiveness of the transfection by simply introducing a tagged

antibody and determine if it is binds to the myeloma cell. If there is no binding, then the DNA sequence encoding for the antibody binding protein was not expressed.

Applicant submits that the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co., v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeal summarized the point well when it stated:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." *Ex parte Jackson*, 217 USPQ 804, 807 (1982).

Here, all the Office has established is that some experimentation would be required to make and use other constructed antibody binding proteins.

The specification provides ample guidance for determining the expression of transfected expression vectors and successful generation of hybridoma cells. It should be noted that claim 1 and all claims depending therefrom defines parameters that enable broader antibody binding proteins because the claims recites functional language that clearly defines the functional activity of the antibody binding protein. According to the court in *In re Marks,* 12 USPQ2d 1904 (BPAI 1989) with the addition of functional language, one skilled in the art would be able to determine in a routine fashion, without undue experimentation whether the antibody binding protein is expressed and functionally active. The functional activity can be very easily determined by one skilled in the art, and the specification provides guidance as set forth in Examples 1 and 2. Thus, the breath of the claims is not broader than that described in the specification and the quantity of

experimentation to practice the full scope of the claims does not require undue experimentation.

Clearly, the level of skill in this field is very high, and as such, information known by one skilled in the art will provide ample assistance in practicing the claimed invention and contribute significantly to the enabling scope of the disclosure.

A disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants submit that the specification provides guidance regarding the antibody binding protein and expressly states that this protein must bind an antibody and present same on the cell surface of the hybridoma cell. Expression of the protein on a myeloma cell is within the ability of one skilled in the art. Further, preparing a hybridoma cell that expresses both an antibody and the antibody binding protein is easily accomplished by following the instructions set forth in the examples of the specification. Applicants have not included an example for each and every possible variant of the antibody binding protein but it is well settled in the law that a working example is not required for every single embodiment of the invention, especially if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice (See *In re Borkowski*, 164 USPQ 642 (CCPA 1970) and *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Thus, the breath of the claims is not broader than that described in the specification and the quantity of experimentation to practice the full scope of the claims does not require undue experimentation.

Applicants request that this rejection under 35 U.S.C. §112, first paragraph for lack of enablement be withdrawn.

3. Claims 21-24 were rejected under 35 U.S.C. §112, first paragraph, because the instant claims contain subject matter which was not described in the specification, as originally filed, in such a way to as to reasonably convey to one skilled in the relevant art that the inventor at the time the application was filed, had possession of the invention as now claimed. In response, applicants have amended independent claim 21 to recite that an animal is immunized with a specific antigen and then spleen material is used to isolate the lymphocytes for fusion with the myeloma cell.

Applicants believe that this amendment of claim 21 obviates the rejection of claims 21-24. As such, applicants request the withdrawal of this rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-14 and 21-24 were as rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants have amended claims 1, 21 and 24 thereby obviating the rejection. Withdrawal of this rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

Conclusion

Applicants have satisfied all the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Grun reconsider the patentability of all pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the

event that any issues remain, Examiner Grun is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

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